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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,950	07/07/2000	George R. Pettit	5368-US	4557

7590 06/17/2003

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EXAMINER
VOLLANO, JEAN F

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/17/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/582,950	PETTIT ET AL.	
	Examiner	Art Unit	
	Jean F. Vollano	1621	

-- The MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-40* is/are pending in the application.

4a) Of the above claim(s) *11,12,22-30 and 34-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-21 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The RCE filed June 5, 2003 has been entered in part. The information disclosure has been entered.

The section that was not entered was a Figure to take the place of a figure shown on top of page 7 of the originally filed specification. The figure was illegible since it seemed to have two or three typing words on top of another. Therefore it was not entered. To have this figure entered please rewrite the request and provide a legible structure.

2. Applicant is reminded that an RCE, unlike a CPA, is a straight continuation and the invention cannot be changed from what was examined in the original examination. The claims cannot be to new subject matter or broadened beyond what was searched both in compounds and processes.

The original examination was an examination of a method of synthesis by "admixing combretastatin A-4 with a phosphorylating agent to form an phosphate ester of combretastatin A-4... selectively cleaving said phosphate ester protective groups with iodotrimethylsilane and treating said phosphorus derivative of combretastatin A with sodium methoxide to yield ..."

This is one of three original claims that was examined. The process other include the steps of dissolving the combretastatin A-4 in acetonitrite;

cooling the solution to 25^0F;

and adding carbon tetrachloride to the cooled solution with stirring; adding 4-dimethylaminopyridine and dibenzyl phosphate to the cooled solution and warm to room temperature

extacting the solvent... admixing chlorotrimethyl silane ... separating the solvent... dissolving in methanol, adding sodium methoxide .. And removing methanol...

The last independent claim was to a compound found in claim 9 which was a cis alkenylene not a trans. .

There was no pharmaceutical composition claimed in the original claimed invention and the pharmaceutical area which is class 514, various subclasses was not searched since there was no pharmaceutical composition.

Claims 31 and 33 are broader than the compound claimed in the original claimed invention in claim 9 and to start this will be restricted into various groups which will include the originally examined group.

Group I claim 31, 32, 33 (in part) drawn to a compound of formula VI wherein X is cis -CH=CH- wherein Q is an alkali metal, or is calcium or magnesium from the alkaline earth metals. (Please note the term is alkaline earth metal, not alkali earth metals. Obviously this is a typographical error -please correct), manganese which is the only transition metal in the original claim, imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline and verapamil. It is noted that the claim as being claimed has left out zinc from the original claim 9 for claim 33 but is improper in claim 32. That

can be added since it was examined. However it is not a transition metal. It has a complete out shell of electrons which precludes it from being a transition metal. The original structure of the compounds as defined in the specification on page 8 give X=H(Z) monovalent or X=X (divalent) with the Z defined on page 8. There are no other combinations that were claimed for the compound and it will be limited to that structure. All other structures which do not fall in this group will be relegated to Group II. It is also noted that there may be new matter with the R1 and R2 structures as related to Q etc. Various classes 558, 556, 548 etc depending on original Y. It is noted that claim 31 and claim 33 would be substantial duplicates if all the non elected subject matter were withdrawn.

Group II claim 31, 32, and 33 (in part) drawn to a compound of formula VI wherein X is cis -CH=CH- and wherein Q is any other moiety found in the claims that is not in Group I. This would be restricted into other groups if this were a first action restriction. However since this is an RCE the group will be as is since it will be removed by original presentation. Various groups and subgroups depending on the Q.

Group III claim 31 and 32 and 33 (in part) drawn to the trans compounds. Again this would be restricted into smaller groups since it falls in classes 556, 560, 564, 540, 536, 549, 558 etc but again it will be withdrawn by original presentation.

Group IV claim 34-35 drawn to a pharmaceutical composition found in class 514 subclasses depend on the structural components.

Group V claim 36 drawn to preparing a compound of structure one by forming a metal salt with phosphoric acid.(This was not an originally claimed process).

Group VI claims 37-39 drawn to a method of modulating tumor growth, found in class 436, 435 etc.

Group VII claim 40 drawn to a method of modulating microbacterial growth in an animal found in class 424, 426, 435 etc.

It is noted that Claim 11 has now broadened the original claim 1 that was searched. The original claim was drawn to the preparation of the sodium salt of the combrestatin see final step . Claim 1 had the limitation of either cis or trans and that would be included. However all the OR choices are not found in the specification but that is irrelevant since the sodium salt was being prepared. Either the mono or disodium salt . Therefore claim 11 was searched to the extent that it read on either cis or trans alkenylene groups wherein OR1 or OR2 are both O^-Q^+ or one of the OR1 or OR2 is hydroxy and the other is O^-Q^+ wherein the Q is sodium or continues from the mono or disodium salt to the compounds of Q found as counter ions in claim 9. However this group will be the non elected group and Q can be anything There is no covalent bonded compounds of OR which would be OQ with the list given by the applicant. The compounds were given as counter ions. However if applicant alleges that they were covalently bonded to specific moieties then please show the point of covalent attachment for the various heterocycles etc. The claim search as claim 1 had an phosphorylating agent to form an ester having protective groups step a) in the invention fits that criteria and in completely part of the process as originally

claimed. However step b is contacting with a trialkyl halo silane. The original claim reacted the compound with iodotrimethyl silane. However the examiner had investigated all trialkyl halo silanes and there for step b) is fine but unfortunately there is no sodium methoxide step which was included in the originally filed process so the claim is not to the originally searched reaction and therefor is in Group VIII is non elected by original presentation which contains claims 11, 12, 14-21, and 30 (in part) are placed in this group. This process would be found in various classes and subclasses including 558 etc.

Group IX which would be claims 13(which includes any of the limitations of claim 11 that was originally given and examined that related to claim 13 so to that extent claim 11 will also be part of the group) that includes the steps a and b in full to prepare the sodium compounds of either cis or trans. This was the original group that was searched. Claim 11 to the extent that it reads on the process of claim 13 , claim 13 and claims 14-21 (in part) and the compounds which are either a disodium or monosodium salt and other compounds claimed as salts that are original found in claim 9.

Group X drawn to making a phosphoric acid compound. Found in class 562 (this process nor this class was search as originally filed). This includes claim 22.

Group XI claims 23-29 is drawn to making a product of formula III by a second process which includes an phosphine reaction followed by an oxidizing step. This process is different from the process claimed in GroupVIII and was not originally claimed.

The compounds of the various compound groups are all patentably distinct since they are not obvious variants and finding one such as found in the 102(b) rejection below would not obviate a rejection of the other groups. The processes are all distinct in that they make different products by different methods and to find each product and each method on line and in the classes and subclasses would be a burdensome search.

The examiner notes at this time that the original claims were written in a confusing manner and the new claims are claiming in such a way that at time they partial overlap and at other times they don't and the examiner will be available if applicant has any questions concerning the groupings or election.

3. Newly submitted claims 11-12, 22-30, and 34-40 are directed to an invention that is independent or distinct from the invention originally claimed for the reasons given above.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, Groups II-VIII, X-XI 11-12, 22-30 and 34-40 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Groups I claims 31-33 (in part) and Group IX , 13 (in full) and 14-21(in part) have been searched to the extent that they read on the originally filed claim. If there is any confusion please call the examiner for clarification.

For clarity the examiner will be examining the process of Claims 13 for preparing the sodium mono or disodium salt that was prepared in original claim 1 the steps can include all the steps that are presently in claim 11 as they are written. However the step in claim 13 must also be in the independent claim so it will be in the same scope of the original claim. Applicant had in claim 1 that the ultimate product was formed by the sodium methoxide step. However there were additional claims wherein the ultimate product was also given as imidazole etc see 6 and 7. This was not really proper since there was no method step given for how to proceed from the sodium salt to the other compounds and were really not further limiting since the "ultimate product" was originally sodium and then was changed to a Y and Z that did not exist . It is not clear if original claims 6 and 7 were on the way to preparing the sodium or where prepared as further comprising after the sodium. The language in the claims was very confusing at best. If applicant would like these products to be in the process claim please include process steps from the sodium salt for further comprising steps. The examiner has examined making the sodium salt per the process of claim 13 which includes the steps a) and b) as given or written in claim 11 and step c) ? which is found claim 13 the combination of these steps and the dependent steps to this process in claims 14-21 to form the mono sodium salt or the disodium salt is not anticipated or suggested by the prior art and if other counter ions would be made from this process (see claim 21) they should be given in a further comprising claim with and actual step or steps being given and they would be considered.

Claim Rejections - 35 U.S.C. § 112

4. Claims 13-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 11 to the extent that it is part of claim 13 recites a step a) and a step b). The wording of step a including an acylation catalyst and di(arylmethyl) phosphite (I can only find a benzyl phosphite) and tetra halomethane are terms that have been broadened in the original claims. Applicant has not shown support for these limitations and the combinations together and the examiner cannot find this generalization in the specification. Therefore it is considered new matter until support is shown commensurate in scope with what is being claimed . Also the term Q is not found in the specification nor is -O-Q found. The compounds were all given as salts and therefore this also is new matter. On page 6 of the specification it states that "Both the sodium and other phosphate salt derivatives of combretastatin Z-4 described herein". Also on page 9 the specification states "the prime object of the subject invention is to prepare prodrugs ... which are both water soluble and stable". The compounds wouldn't be water soluble if they weren't salts for example if verapamil were combined in a covalent manner it would be less water soluble then the acid precursor which the specification says is not soluble.

The wording "a period of time sufficient to generate the phosphoric acid compound" is also not found in the specification. This is along with transition metal and other terms are not

found in claim 11. Also where is the combination of the diarylmethyl phosphite, the terahalomethane, a tertiary amine and an acylation catalyst together come from in the specification? Also the terms heterocycle and nucleoside, alkaloid. These seem to be lacking in the specification.

The limitation wherein the solvent is halogenated or non a halogenated cannot be found . Most of the new limitations that broaden what was originally claimed cannot be found in the specification. Please give support for these changes.

5. Claims 13 and 16, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 to the extent that it also contains the limitations found in claim 11 recites the limitation of "wherein R3 is an arylmethyl phosphate protecting group. There is no aryl methyl phosphate protecting group. R3 is a arylmethyl group. The way it is worded it seems that the phosphorus is part of the protecting group.

Claim 16 recites DBU there is no explanation of what the term refers to. Claim 16 also states where the tertiary amine is selected from ... pyridine, N methyl morpholine and DBU. It is not clear what DBU is but for sure pyridine and morpholine are not tertiary amines.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Pettit (US5561122).

When Pettit discloses the compound of the combretastatin A4 phosphate sodium salt (example 2, page 11) the claim is fully anticipated.

8. Claims 31 and 33 rejected under 35 U.S.C. 102(b) as being anticipated by Pettit et al (Anti Cancer Drug Design 1995).

When Pettit discloses the compound of the combretastatin A4 phosphate or sodium salt (examples on page 104) the claim is fully anticipated.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over anticipated by Pettit (US5561122).

Pettit compound of the combretastatin A4 phosphate sodium salt and the potassium salt (example 2, page 11).

Pettit does not teach the lithium or cesium salt. However since the potassium and sodium salt are easily formed by interaction of a phosphorus acid with a sodium or potassium source to form a biologically active compound that is a salt of Group I alkali metals then it would have been obvious to one of ordinary skill in the art to have made another Group I metal salt by exchanging another Group I alkali metal which is a lithium or a cesium to form addition Group I alkali metal salts with the expectation that they would also be biologically active since two of the alkali metal salts are already known to be biologically active. The other motivation is to have a compound that is biologically active that is also water soluble and the salts give the compound that property no matter which alkali metal salt it is. The activity is essentially in the anion. The cation (i.e. alkali metal salt is just present to help the anion dissolve and then become available for activity).

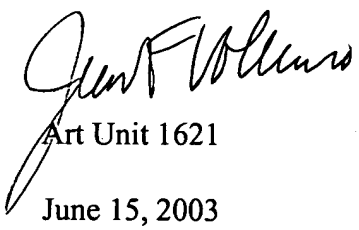
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr J F Vollano whose telephone number is (703) 305-4483. The examiner can normally be reached on Monday to Thursday from 6:30 to 5:00 .

12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter , can be reached on (703)308-4532 . The official fax phone number for the organization where this application or proceeding is assigned is (703)308-4556. It should be noted that the examiner cannot immediately work on a fax sent to this number.

13. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-1235.

Jean F. Vollano

Primary Examiner



Art Unit 1621

June 15, 2003